INSULIN AND AMINO ACID INFUSION AFTER CARDIAC OPERATIONS: EFFECTS ON SYSTEMIC AND RENAL PERFUSION

Anders Jeppsson, MD[a]
Rolf Ekroth, MD, PhD[a]
Klaus Kirnö, MD, PhD[b]
Italo Milocco, MD, PhD[b]
Boris Nilsson, MD[a]
Folke Nilsson, MD, PhD[a]
Sveneric Svensson, MD, PhD[a]
Jan Wernerman, MD, PhD[c]

Objective: **The purpose of this study was to answer two questions: (1) Does a mixed amino acid infusion enhance systemic and renal perfusion in the early postoperative period after heart operations? (2) Does the addition of insulin (glucose-insulin-potassium solution) provide additional effects to those of an amino acid infusion?** ***Methods:*** **Thirty-three male patients undergoing coronary artery bypass grafting (mean age 65.9 ± 1.2 years) were included in a prospective, controlled, randomized study. Eleven patients (AA group) received infusion of mixed amino acids (11.4 gm), 11 patients (AA + GIK group) received infusion of mixed amino acids (11.4 gm) and insulin solution (225 IU insulin, glucose with glucose clamp technique, and potassium), and 11 patients served as control subjects.** ***Results:*** **Amino acid infusion alone had no effect on systemic vascular resistance or cardiac index but increased renal blood flow 51% ± 11% (from 114 ± 13 to 172 ± 24 ml · min^{-1} · m^{-2} in one kidney, $p < 0.05$ vs the control group). Insulin solution in addition to amino acid infusion reduced systemic vascular resistance 24% ± 3% (from 1280 ± 85 to 960 ± 57 dyn · sec · cm^{-5}, $p < 0.05$ vs the control and AA groups) and increased cardiac index 13% ± 3% (from 2.3 ± 0.2 to 2.6 ± 0.2 L · min^{-1} · m^{-2}, $p < 0.05$ vs the control and AA groups). Insulin had no significant additive effect on renal blood flow.** ***Conclusions:*** **Our data imply that (1) infusion of mixed amino acids enhances renal blood flow after cardiac operations but has no effect on systemic perfusion and (2) the addition of insulin solution improves systemic perfusion. The combined treatment may potentially reduce the risk of renal hypoperfusion injury in the postoperative period after coronary artery bypass grafting. (J Thorac Cardiovasc Surg 1997;113: 594-602)**

Renal dysfunction is common in the postoperative period after cardiac operations. When the renal dysfunction is severe enough to necessitate dialysis, the prognosis is dismal with a mortality rate close to 40%.[1] In the majority of cases, renal dysfunction is caused by renal hypoperfusion with resultant ischemic injury. This may occur before, during, or, probably most important, after the operation. The primary event is most commonly low output heart failure.[2] The kidneys may be at particular risk during systemic hypoperfusion inasmuch as surgical trauma per se induces redistribution of systemic blood flow with a smaller proportion of cardiac output perfusing the kidneys.[3]

At most centers the treatment of postoperative low output syndrome is based on adrenergic support. One drawback of this therapeutic approach is that high doses of most inotropic agents tend to cause vasoconstriction and may thus aggravate renal ischemic injury. Alternative approaches to treat myocardial dysfunction and heart failure are the use of insulin (in combination with glucose and potas-

From the Departments of Thoracic and Cardiovascular Surgery[a] and Anesthesiology,[b] Sahlgrenska University Hospital, Göteborg, Sweden, and the Department of Anesthesiology,[c] Huddinge University Hospital, Huddinge, Sweden.

Supported by grants from Sahlgrenska University Hospital, Göteborg Medical Society, The Swedish Medical Society, Nils Gunnarsson's Legacy, and Pharmacia-Upjohn, Stockholm, Sweden.

Received for publication Feb. 26, 1996; revisions requested July 9, 1996; revisions received Sept. 6, 1996; accepted for publication Oct. 23, 1996.

Address for reprints: Anders Jeppsson, MD, Department of Thoracic and Cardiovascular Surgery, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.

0022-5223/97 $5.00 + 0 **12/1/78760**

sium, that is, glucose-insulin-potassium [GIK] solution),[4, 5] infusion of amino acids such as glutamate,[6] or use of both these methods. These agents may be beneficial also from the aspect of renal hypoperfusion, because both insulin and various amino acids can decrease renal vascular resistance (RVR) and enhance renal blood flow (RBF) during nonsurgical conditions.[7, 8] The effects of these agents on renal perfusion, if any, in conjunction with cardiac operations, are unknown.

The purpose of this study was to answer two questions: (1) Does a mixed amino acid infusion enhance systemic and renal perfusion in the early postoperative period after heart operations? and (2) Does the addition of insulin (GIK solution) provide additional effects to those of an amino acid infusion?

Patients and methods

Patients. Patients included in the study met the following inclusion criteria: male gender, age 40 to 80 years, two- or three-vessel coronary disease with stable angina and appropriate condition for coronary operations, left ventricular ejection fraction greater than 40%, no other significant disorders, and serum creatinine level less than 15 mg/L. Exclusion criteria were perioperative myocardial infarction, postoperative low output heart failure, and the use of inotropic, vasoactive, or diuretic agents. Thirty-four patients were originally included in the study. One of these was excluded after the second measurement period (before treatment was initiated) because of electrocardiographic signs of perioperative myocardial infarction. Characteristics of the remaining 33 patients are listed in Table I. The study protocol was approved by the Research Ethics Committee of the Medical Faculty, University of Göteborg. Informed consent was given by all patients.

Clinical management. The patients were given premedication consisting of flunitrazepam and morphine/scopolamine. Anesthesia was induced with thiopental, 3 to 5 mg/kg, followed by pancuronium, 0.1 mg/kg. Fentanyl was given in incremental doses up to a total amount of 8 to 10 μg/kg before sternotomy. Normal parameters were used for ventilation of the lungs with oxygen in air (fraction of inspired oxygen 0.4 to 0.5), and enflurane was used as an inhalational agent both before and after cardiopulmonary bypass. Midazolam was given during cardiopulmonary bypass.

The operations were done with a standard nonpulsatile cardiopulmonary bypass technique, with moderate hypothermia (nasal temperature 30° C) and hemodilution (hematocrit level 20% to 30%). Cardioprotection was achieved with St. Thomas' Hospital crystalloid cardioplegic solution. Weaning from bypass was done after the patient was rewarmed to a rectal temperature of at least 36° C.

Study protocol. Before the operation, a femoral artery catheter and a Swan-Ganz pulmonary artery catheter (Baxter Healthcare Corp., Edwards Division, Santa Ana, Calif.) were inserted for continuous monitoring of systemic and pulmonary arterial pressures, for measuring cardiac output, and for blood sampling. A thermodilution catheter (Webster Laboratories, Baldwin Park, Calif.) was inserted under fluoroscopic guidance, with the distal mixing thermistor placed in a central position in the left renal vein. The position of the catheter was checked after the operation.

Table I. *Patient characteristics*

	Group		
	AA (n = 11)	*AA + GIK (n = 11)*	*Control (n = 11)*
Age (yr)	63.3 ± 2.2	66.6 ± 1.8	64.2 ± 2.7
Body surface area (m^2)	1.99 ± 0.07	1.99 ± 0.04	1.99 ± 0.06
Body weight (kg)	84 ± 5.6	81 ± 3.9	85 ± 4.1
Preoperative left ventricular ejection fraction (%)	61 ± 5	63 ± 2	64 ± 3
Coronary disease (2-vessel/3-vessel)	9/2	8/3	9/2
Serum creatinine level (mg/L)			
Preoperative	11.4 ± 0.5	11.5 ± 0.5	11.6 ± 0.5
Peak postoperative	11.2 ± 0.6	12.2 ± 1.0	12.0 ± 0.7
At hospital discharge	10.3 ± 0.5	10.9 ± 0.7	10.0 ± 0.5
Aortic crossclamping (min)	51 ± 5	46 ± 4	53 ± 6
Extracorporeal circulation (min)	90 ± 6	86 ± 5	88 ± 6
Peripheral anastomoses (No.)	3.4 ± 0.2	3.3 ± 0.1	3.4 ± 0.2
Days in hospital	7.0 ± 0.4	7.1 ± 0.4	7.4 ± 0.4

Values given as mean plus or minus the standard error of the mean. There was no significant difference among the groups.

Hemodynamic measurements were taken at three preset times: before the operation, immediately after the operation (in the operating room after skin closure, with satisfactory clinical hemodynamic variables, that is, mean arterial pressure [MAP] >60 mm Hg, urinary output >2 ml/kg of body weight per hour, and mixed venous oxygen saturation >60%), and after 30 minutes of infusion (which continued while the measurements were taken).

After the first postoperative measurements were taken the patients were randomized to one of three groups. The AA group received an infusion of mixed amino acids (Vamin 18 gm nitrogen per liter, Pharmacia, Stockholm, Sweden, 200 ml/hr, composition given in Table II). The AA + GIK group received mixed amino acids and GIK solution (Vamin 18 gm nitrogen per liter, 200 ml/hr; Actrapid insulin, Novo Nordisk, Bagsvaerd, Denmark, 100 units as a bolus dose followed by 250 IU/hr; glucose 30%, 75 ml/hr initially and then adjusted according to blood glucose measurements; and potassium 10 mmol/hr). The third group served as control subjects.

Hemodynamic measurements. MAP and central venous pressure were measured continuously. Cardiac output was determined by the thermodilution technique. Pulmonary capillary wedge pressure (PCWP) was measured immediately before each cardiac output measurement. RBF was determined by the retrograde thermodi-

Table II. *Content of the mixed amino acid solution*

	Grams per 1000 ml
Alanine	16.0
Arginine	11.3
Aspartate	3.4
Cysteine	0.56
Glycine	7.9
Glutamate	5.6
Histidine	6.8
Isoleucine	5.6
Leucine	7.9
Lysine	9.0
Methionine	5.6
Phenylalanine	7.9
Proline	6.8
Serine	4.5
Threonine	5.6
Tryptophan	1.9
Tyrosine	0.23
Valine	7.3

lution technique originally described by Hornych, Brod, and Slechta[8a] and modified by Tidgren and Hjemdahl.[9]

Systemic vascular resistance (SVR) was calculated with the formula SVR ($dyn \cdot sec \cdot cm^{-5}$) = 80 × (MAP − CVP)/CO, where CVP is central venous pressure and CO is cardiac output. Left ventricular stroke work index (LVSWI) was calculated according to the formula LVSWI ($gm \cdot m)/m^2$/beat) = 13.6 × (CI/HR) × (MAP − PCWP), where CI is the cardiac index and HR is the heart rate. RVR was calculated according to the formula RVR (mm $Hg \cdot L^{-1} \cdot min^{-1}$) = (MAP − CVP)/RBF, where central venous pressure (CVP) was assumed to be representative also for renal venous pressure. Renal fraction of blood flow (RF) was calculated with the formula RF (%) = 2 × RBF/CO, where CO is cardiac output and equal flow in both kidneys was assumed. All flow values were related to body surface area.

Arterial concentrations of insulin and amino acids. Insulin and amino acid concentrations in arterial plasma were measured after 30 minutes of infusion. The concentrations of amino acids were determined by ion exchange chromatography with use of an automated amino acid analyzer (Alpha Plus, LKG Products, Bromma, Sweden) using DC-6 ion exchange resin (Durrum, Calif.) and lithium citrate buffers. Orthophtaldialdehyde was used for post-column derivation and fluorescent detection (Shimatsu RF-535) at an excitation wavelength of 350 nm and an emission wavelength of 420 nm.

Insulin level was assessed by a radioimmunoassay method (Insulin RIA-100, Pharmacia, Uppsala, Sweden).

Statistical analysis. The patients were randomized to one of the three study regimens by a computerized procedure of sequential allocation[10] including the patient's age, weight, preoperative serum creatinine concentration, bypass time, aortic clamp time, postoperative CI, postoperative heart rate, and postoperative PCWP. To establish whether the randomization had provided groups that were comparable before treatment, intergroup comparisons of the first and the second measurements ("control periods") were done with one-way analysis of variance.

To evaluate effects of amino acids and insulin, intergroup comparisons of intragroup changes between the two postoperative measurements (before and during treatment) were done with one-way analysis of variance. If analysis of variance indicated statistical intergroup difference ($p < 0.05$), Duncan's multiple range test was done.

Student's t test was used to evaluate the difference in arterial insulin concentration between the AA group and the control group. In the AA + GIK group the insulin concentrations were 200- to 1000-fold higher than those in the other groups, which made the three-group variance analysis insufficient. The analysis was also insufficient concerning the arterial concentrations of amino acids, which were twofold to threefold higher in both treatment groups than in control subjects. In this comparison we used Student's t test to evaluate the difference between the AA and AA + GIK groups.

Standard regression analysis was used to evaluate possible hemodynamic predictors of CI and RBF.

One-way analysis of covariance was done with group and PCWP changes (Table III, column 4) as predictors and CI as responder.

Statistical significance was defined as $p < 0.05$.

Results

Clinical course. All patients recovered normally after the operation and were discharged from the hospital within 10 days after the operation. One patient in the AA + GIK group had a transient elevation of the serum creatinine level up to 31.8 mg/L, whereas serum creatinine levels in all the other patients were unchanged or had a transient increase within 25%.

Pretreatment systemic and renal variables (Table III, columns 2 and 3). There were no significant differences between the groups in pretreatment systemic and renal variables.

Effects of treatment (Figs. 1 through 3)

Arterial concentrations of insulin and amino acids. The insulin levels in arterial serum differed among the three groups. The concentration in the AA group was 54 ± 11 $mU \cdot L^{-1}$ ($p < 0.01$ vs control subjects), in the AA + GIK group 10,345 ± 1396 $mU \cdot L^{-1}$, and in the control group 13 ± 2 $mU \cdot L^{-1}$. The arterial concentrations of amino acids are given in Table IV. The levels were twofold or threefold higher in the treatment groups compared with those in control subjects with no overlap. There was no difference between the AA and AA + GIK groups.

Systemic hemodynamic variables (Table III, column 5). The amino acid infusion alone (AA group) had no effects on systemic vascular resistance, CI, PCWP, or MAP. In the AA + GIK group systemic vascular resistance decreased 24% ± 3% ($p < 0.05$

Table III. *Hemodynamic variables before operation, immediately after operation, and after 30 minutes of infusion in AA group and in AA + GIK group*

	Before operation	*After operation*	*During infusion*	Δ	*ANOVA (Δ)*	*Duncan (Δ)*
SVR (dyn·sec·cm^{-5})					$p = 0$	
AA	1631 ± 122	1147 ± 67	1178 ± 97	31 ± 90		
AA + GIK	1649 ± 102	1280 ± 85	960 ± 57	−292 ± 48		$p < 0.05$ vs AA and control groups
Control	1472 ± 58	1114 ± 96	1251 ± 91	136 ± 42		
CI (L/min^{-1})					$p = 0.007$	
AA	1.7 ± 0.1	2.6 ± 0.1	2.5 ± 0.2	0.0 ± 0.1		
AA + GIK	1.7 ± 0.1	2.3 ± 0.1	2.6 ± 0.2	0.3 ± 0.1		$p < 0.05$ vs AA and control groups
Control	1.8 ± 0.1	2.5 ± 0.2	2.4 ± 0.2	−0.1 ± 0.1		
MAP (mm Hg)					$p = 0.002$	
AA	77 ± 4.3	81 ± 2.4	81 ± 3.3	0 ± 3.7		
AA + GIK	75 ± 2.2	80 ± 3.2	70 ± 2.3	−11 ± 2.2		$p < 0.05$ vs AA and control groups
Control	72 ± 2.2	77 ± 2.4	83 ± 3.0	6 ± 3.3		
CVP (mm Hg)					NS	
AA	9 ± 0.8	10 ± 0.9	11 ± 0.7	0.4 ± 0.8		
AA + GIK	8 ± 0.8	11 ± 0.7	11 ± 0.7	−0.3 ± 0.4		
Control	7 ± 0.7	10 ± 0.6	11 ± 0.9	0.9 ± 0.5		
PCWP (mm Hg)					NS	
AA	11 ± 1.2	12 ± 0.8	14 ± 0.8	1.6 ± 0.5		
AA + GIK	11 ± 1.4	12 ± 1.0	13 ± 1.2	0.3 ± 0.9		
Control	10 ± 1.2	12 ± 0.9	13 ± 1.2	1.1 ± 0.9		
Heart rate (beats/min)					NS	
AA	53 ± 2	78 ± 3	78 ± 4	0.1 ± 0.9		
AA + GIK	58 ± 3	75 ± 4	78 ± 2	3.0 ± 2.1		
Control	55 ± 3	77 ± 5	77 ± 4	0.6 ± 1.7		
LVSWI (gm·m/m^2/beat)					NS	
AA	29 ± 1.6	31 ± 1.0	30 ± 2.4	−0.7 ± 2.4		
AA + GIK	25 ± 1.3	28 ± 2.5	26 ± 2.0	−2.5 ± 1.1		
Control	29 ± 2.5	29 ± 2.4	30 ± 2.2	0.7 ± 2.1		
RVR (mm Hg·L^{-1}·min^{-1})					$p = 0.015$	
AA	527 ± 124	377 ± 57	258 ± 38	−119 ± 39		
AA + GIK	525 ± 93	515 ± 88	255 ± 36	−259 ± 70		$p < 0.05$ vs control group
Control	424 ± 66	349 ± 57	358 ± 57	11 ± 68		
RBF (ml · min^{-1} · m^{-2})					$p = 0.013$	
AA	98 ± 17	114 ± 13	172 ± 24	58 ± 15		$p < 0.05$ vs control group
AA + GIK	83 ± 12	86 ± 12	135 ± 13	49 ± 9		$p < 0.05$ vs control group
Control	102 ± 18	131 ± 25	133 ± 26	−10 ± 22		
RBF/CI (%)					$p = 0.032$	
AA	11 ± 1.7	9 ± 1.0	14 ± 2.1	4.9 ± 1.5		$p < 0.05$ vs control group
AA + GIK	10 ± 1.2	8 ± 1.1	11 ± 1.4	3.2 ± 1.0		
Control	11 ± 1.8	11 ± 2.6	11 ± 2.1	−1.0 ± 2.0		
Hb (gm·L^{-1})					$p = 0.013$	
AA	132 ± 3	104 ± 3	104 ± 4	−0.5 ± 1.6		
AA + GIK	132 ± 4	104 ± 4	101 ± 3	−3.4 ± 1.1		$p < 0.05$ vs control group
Control	135 ± 4	110 ± 5	112 ± 5	2.5 ± 1.2		

Values given as mean plus or minus the standard error of the mean. Intergroup comparisons in column 1 and in column 2 were done with one-way variance analysis (ANOVA). There were no statistical differences. The values in column 4 (Δ, the difference between the two postoperative measurements, before and during treatment) are compared with one-way variance analysis (ANOVA) and, when $p < 0.05$, followed by Duncan's multiple range test. Statistical differences between the group changes (Δ) are indicated. *SVR,* Systemic vascular resistance; *CVP,* central venous pressure; *NS,* not significant; *LVSWI,* left ventricular stroke work index; *Hb,* arterial content of hemoglobin.

vs control and AA groups), CI increased 13% ± 3% ($p < 0.05$ vs control and AA groups), and MAP decreased 13% ± 2% ($p < 0.05$ vs control and AA groups). There were no differences in left ventricular stroke work index between the groups. There was no significant correlation between changes in PCWP and CI ($r = 0.15$). Analysis of covariance indicated that group had an effect on CI ($F = 8.18$, degree of

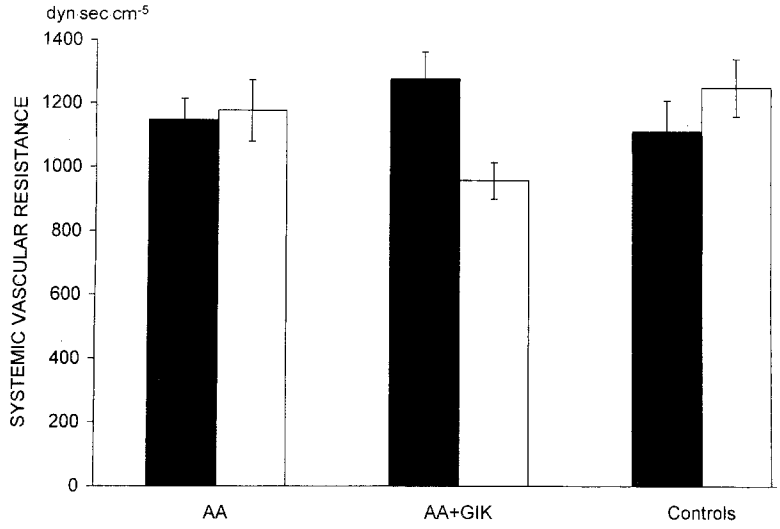

Fig. 1. Systemic vascular resistance before *(black bars)* and during *(white bars)* infusion of amino acids in the AA group ($n = 11$) and infusion of amino acids and GIK solution in the AA + GIK group ($n = 11$). The control group ($n = 11$) did not receive any treatment. Statistical evaluation of treatment is given in Table III.

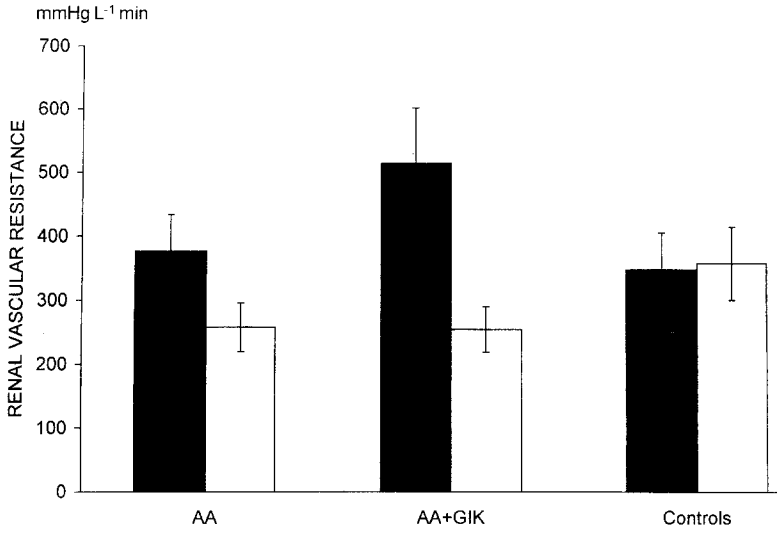

Fig. 2. RVR before *(black bars)* and during *(white bars)* infusion of amino acids in the AA group ($n = 11$) and infusion of amino acids and GIK solution in the AA + GIK group ($n = 11$). The control group ($n = 11$) did not receive any treatment. Statistical evaluation of treatment is given in Table III.

freedom = 2, $p < 0.001$) and that PCWP changes affected CI response ($F = 5.04$, degree of freedom = 1, $p = 0.03$). The slopes were equal ($F = 0.20$, degree of freedom = 2, $p = 0.82$).

Renal hemodynamic variables (Table III, column 5). The amino acid infusion alone increased RBF 58 ± 15 ml · min^{-1} · m^{-2} (one kidney), corresponding to a 51% ± 11% increase ($p < 0.05$ vs control subjects). RVR decreased numerically in the AA group, but the change did not differ significantly from the control values according to Duncan's multiple range test. The addition of insulin (GIK solution) did not increase RBF further. It increased 49 ± 9 ml · min^{-1} · m^{-2} (one kidney), corresponding

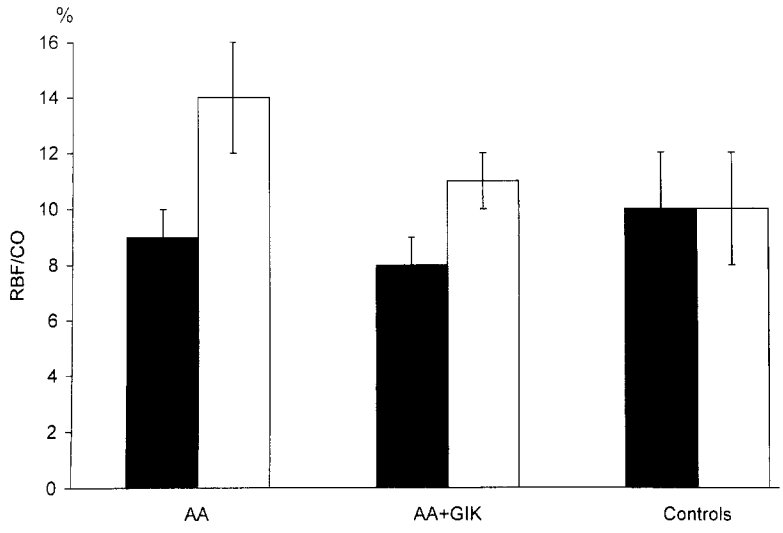

Fig. 3. Renal fraction of cardiac output *(RBF/CO)* before *(black bars)* and during *(white bars)* infusion of amino acids in the AA group (n = 11) and infusion of amino acids and GIK solution in the AA + GIK group (n = 11). The control group (n = 11) did not receive any treatment. Statistical evaluation of treatment is given in Table III.

to a 73% ± 19% increase ($p < 0.05$ vs control subjects). In the AA + GIK group RVR decreased significantly versus the control group. However, the analysis indicated that there was no difference between the AA and AA + GIK groups. The renal fraction (RBF/cardiac output) increased in the AA group from 9% ± 1% to 14% ± 2% ($p < 0.05$ vs control group). There was no significant correlation between changes in MAP and RBF ($r = -0.23$) or between changes in CI and RBF ($r = 0.02$).

Discussion

These data indicate that the addition of insulin (GIK solution) to a mixed amino acid infusion enhances systemic and renal perfusion in the postoperative period after cardiac operations in patients with an uncomplicated postoperative course. The mixed amino acid infusion alone improved renal perfusion equally well, but had no effects on systemic hemodynamic variables. This suggests that the use of amino acids and GIK solution may provide a treatment for low output heart failure after cardiac operations, which may reduce the risk of renal hypoperfusion injury. However, the suggestion prompts follow-up studies in patients with higher risk conditions.

Methodologic issues. The study design may be debated. The first issue is the selection of patients. We chose patients who we anticipated would have an uncomplicated postoperative course, without need for inotropic, vasoactive, or diuretic agents. This was done to facilitate the evaluation of amino acid and GIK treatments. It is appreciated that the selection restricts the validity of conclusions to this patient category. However, we reasoned that a pilot study of patients at low risk would be valuable for the design of subsequent studies in patients who are more at risk for the development of heart and renal failure.

Another aspect of the current protocol is the two alternative treatments. It could be argued that the effects of insulin should have been studied without the infusion of amino acids. Amino acids may have concealed insulin-induced renal vasodilation. However, insulin alone reduces the plasma concentration and intracellular content of most amino acids.[11] We reasoned that it could be even more difficult to evaluate the effects of insulin per se at a reduced availability of amino acids, because this could have obviated true effects of insulin. With the present protocol, amino acid levels were elevated in both treatment groups to ascertain that the availability of amino acids was unrestricted. With some reservation, it should be possible to evaluate insulin effects by subtracting the effects of amino acid infusion alone from the combined effect of insulin (GIK solution) and amino acid infusion. This reasoning may not be valid, however, if insulin and amino acid effects have a common mediator.

Table IV. *Arterial concentrations of amino acids after 30 minutes of infusion in AA group and in AA + GIK group*

	Concentration (μg/L)
Alanine	
AA	942 ± 97
AA + GIK	1090 ± 95
Control	242 ± 28
Arginine	
AA	462 ± 60
AA + GIK	468 ± 19
Control	85 ± 7
Aspartate	
AA	80 ± 11
AA + GIK	75 ± 3
Control	4 ± 0.4
Citrulline	
AA	35 ± 7
AA + GIK	36 ± 4
Control	26 ± 2
Glutamate	
AA	383 ± 48
AA ± GIK	303 ± 16
Control	80 ± 6
Glutamine	
AA	559 ± 46
AA + GIK	635 ± 27
Control	470 ± 31
Glycine	
AA	598 ± 63
AA + GIK	687 ± 20
Control	167 ± 20
Histidine	
AA	271 ± 28
AA + GIK	310 ± 7
Control	80 ± 5
Isoleucine	
AA	313 ± 27
AA + GIK	301 ± 12
Control	63 ± 2
Leucine	
AA	489 ± 43
AA + GIK	473 ± 19
Control	149 ± 6
Methionine	
AA	169 ± 22
AA + GIK	176 ±4
Control	16 ± 2
Ornithine	
AA	108 ± 13
AA + GIK	108 ± 6
Control	48 ± 4
Phenylalanine	
AA	236 ± 23
AA + GIK	251 ± 8
Control	52 ± 4
Serine	
AA	260 ± 29
AA + GIK	296 ± 11
Control	82 ± 11
Taurine	
AA	83 ± 8
AA + GIK	72 ± 5
Control	64 ± 3
Threonine	
AA	327 ± 40
AA + GIK	370 ± 17
Control	95 ± 11
Tryptophan	
AA	84 ± 15
AA + GIK	88 ± 7
Control	31 ± 4
Tyrosine	
AA	88 ± 12
AA + GIK	83 ± 3
Control	55 ± 5
Valine	
AA	665 ± 55
AA + GIK	669 ± 22
Control	271 ± 12

Values given as means plus or minus the standard error of the mean.

Another matter of concern is the technique for RBF measurement. The clinically most commonly used method is based on renal clearance of para-aminohippurate. The technique requires urine sampling, which reduces the temporal resolution of this method. In contrast, the thermodilution technique has considerably better temporal resolution, and its validity in surgical conditions has been verified by previous work.[9] Furthermore, the extraction of para-aminohippurate is lower than normal in conjunction with cardiac operations (80% to 85% compared with the normal 90% to 95%), which reduces the sensitivity of the para-aminohippurate technique.

The RBF values after the operation were generally higher than those before the operation. Theoretically this could be the effect of changed catheter position. The risk of catheter displacement was appreciated and the position was checked after the operation. A more probable explanation relates to the 20% lower hemoglobin level after the operation, with a low oxygen content, which necessitates a higher flow to maintain oxygen supply, and the lower viscosity, which reduces flow resistance.

Effects of amino acid infusion. The amino acid infusion had no effect on systemic hemodynamic variables. This finding contrasts to that of previous work, which indicated that glutamate increases cardiac output[6] and that arginine induces vasodila-

tion.[12] Both glutamate and arginine were present in the infusion (9.9% and 4.9%, respectively, of the amino acid content) and arterial plasma concentrations were increased more than threefold and fourfold, respectively. Even so, it may be suspected that higher doses of these amino acids are required to obtain systemic hemodynamic effects. The amino acid infusion, however, increased RBF as well in the current context. RVR decreased numerically 29%. This was not significantly different from control values, which is puzzling because blood pressures were equal at marked differences in RBF. A type II error may be suspected. In previous work done during nonsurgical conditions, the fall in RVR and the increase in RBF after amino acid administration have been in the 10% to 20% range.[8] In the present study the corresponding values were more than twice as high. The present data cannot explain the amplified response. The early postoperative period is characterized by insulin resistance and renal vasoconstriction (relative to systemic vascular resistance), and it is worth noting that previous workers reported a greater response than normal in patients with diabetes, who have increased RVR.[13]

There is a body of evidence from animal and clinical nonsurgical work that indicates that amino acids reduce RVR and hence increase RBF.[8, 14] The importance of individual amino acids has been debated. According to some investigators arginine, the nitric oxide precursor, is the most potent amino acid, whereas other investigators conclude that other gluconeogenetic amino acids are equally or more potent.[15] The mechanism for amino acid–induced renal vasodilation is unknown. Both systemic humoral factors, such as glucagon, and intrarenal vasodilative agents, such as kallikrein, prostaglandins, dopamine, and endothelium-derived nitric oxide, have been proposed as being the cause for renal vasodilation.[15-19]

The observation that the effects can be accomplished also in the isolated kidney preparation implies a local mediator.[20] The present data indicate that changes in renal perfusion pressure or CI were unrelated to RBF changes during amino acid infusion.

Effects of insulin. The present data confirm that insulin produces systemic vasodilation and increases cardiac output. In vitro work by Lucchesi, Median, and Kniffen[21] indicated that insulin had a positive inotropic effect on the canine heart. Our group reported dose-response data between insulin and hemodynamic parameters over a wide range of insulin dosages (up to 500 IU as a bolus) early after cardiac operations.[22] The studies were done under glucose "clamp" conditions, that is, blood glucose was maintained euglycemic, excluding the possibility that the increases in cardiac output were caused by changes in blood glucose level. The current protocol was based on that experience. The previous work indicated that insulin is a potent vasodilating agent.[5, 23-25] Inotropic effects are difficult to evaluate with the current techniques because of the low specificity. However, there was no difference between groups in left ventricular stroke work index (according to analysis of variance) or in PCWP versus CI slopes (according to covariance analysis). These findings argue against important effects on contractility. Thus it appears that vasodilative effects are more impressive at least in patients with an uncomplicated course. It may be different in patients with overt postoperative heart failure, as indicated by the work of Gradinac and colleagues.[4]

The combined effect of insulin and amino acids resulted in improved renal perfusion with decreased RVR and increased RBF compared with values in control subjects. However, the effects were not greater than those during amino acid infusion alone. Other investigators have shown renal vasodilating effects of insulin,[7, 23] also in the isolated kidney.[26] To explain the lack of effect of insulin in our study different alternatives may be considered. It may be suggested that the vasodilating effect on the kidney is less pronounced and concealed by the marked effect of the mixed amino acid infusion, or the profound insulin resistance in the postoperative period may attenuate the normal response. Alternatively, the effect may be reduced or even absent because of a common mediator that already has been activated maximally by amino acids. Furthermore, infusion of amino acids evokes a release of endogenous insulin.[14] It could be speculated that amino acids are efficient because of endogenous insulin release. If so, the difference in effects on RVR and systemic vascular resistance would suggest different dose-response curves for renal and systemic vasodilation. This speculation is supported by the work of others, which has shown that somatostatin, which blocks insulin release, prevents amino acid renal vasodilation.[8]

Clinical implications and conclusions. Metabolic intervention is a clinical option in the treatment of postoperative heart failure in heart operations. The present data indicate that metabolic intervention with insulin and amino acids also enhances renal perfusion, at least in patients with an uncomplicated

postoperative course. Our finding suggests a new principle for the prevention of acute renal failure in heart operations. Future studies should evaluate the validity of this suggestion in patients with a greater risk of postoperative complications.

Statistical advice was given by Anders Odén, PhD, Kungälv, Sweden. The skillful assistance of Liselott Thunberg, Kerstin Andersson, PhD, and Maria Stålberg is gratefully acknowledged.

REFERENCES

1. Zanardo G, Michielon P, Paccagnella A, et al. Acute renal failure in the patient undergoing cardiac operation: prevalence, mortality rate, and main risk factors. J Thorac Cardiovasc Surg 1994;107:1489-95.
2. Slogoff S, Reul GJ, Keats AS, et al. Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. Ann Thorac Surg 1990;50:911-8.
3. Andersson LG, Bratteby LE, Ekroth R, et al. Renal function during cardiopulmonary bypass: influence of pump flow and systemic blood pressure. Eur J Cardiothorac Surg 1994;8:597-602.
4. Gradinac S, Coleman GM, Taegtmeyer H, Sweeney MS, Frazier OH. Improved cardiac function with glucose-insulin-potassium after aortocoronary bypass grafting. Ann Thorac Surg 1989;48:484-9.
5. Svensson S, Svedjeholm R, Ekroth R, et al. Trauma metabolism and the heart: uptake of substrates and effects of insulin early after cardiac surgery. J Thorac Cardiovasc Surg 1990;99:1063-73.
6. Pisarenko O, Lepilin M, Ivanov V. Cardiac metabolism and performance during L-glutamic acid infusion in postoperative cardiac failure. Clin Sci 1986;70:7-12.
7. Stenvinkel P, Alvestrand A. Insulin causes renal vasodilatation independently of renal prostaglandins in healthy humans. Nephrol Dial Transplant 1994;9:1728-33.
8. Castellino P, Coda B, DeFronzo RA. Effect of amino acid infusion on renal hemodynamics in humans. Am J Physiol 1986;251:F132-40.

8a. Hornych A, Brod J, Slechta A. The measurement of renal venous outflow in man by the local thermodilution method. Nephron 1971;8:17-32.

9. Tidgren B, Hjemdahl P. Renal responses to mental stress and epinephrine in humans. Am J Physiol 1989;257:F682-9.
10. Pocock S, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.
11. Fukagawa N, Minaker K, Young V. Insulin dose-dependent reductions in plasma amino acids in man. Am J Physiol 1986;257:E13-7.
12. Calver A, Collier J, Vallance P. Dilator actions of arginine in human peripheral vasculature. Clin Sci 1991;81:695-700.
13. Tuttle KR, Bruton JL. Effect of insulin therapy on renal hemodynamic response to amino acids and renal hypertrophy in non-insulin-dependent diabetes. Kidney Int 1992;42:167-73.
14. Giordano M, Castellino P, McConnell EL, DeFronzo RA. Effect of amino acid infusion on renal hemodynamics in humans: a dose-response study. Am J Physiol 1994;267: F703-8.
15. Chen C, Mitchell KD, Navar LG. Role of endothelium-derived nitric oxide in the renal hemodynamic response to amino acid infusion. Am J Physiol 1992;263:R510-6.
16. Jaffa AA, Vio CP, Silva RH, et al. Evidence for renal kinins as mediators of amino-acid-induced hyperperfusion and hyperfiltration in the rat. J Clin Invest 1992;89:1460-8.
17. Hirshberg RR, Zipser RD, Slomowitz LA, Kopple JD. Glucagon and prostaglandins are mediators of amino-acid-induced rise in renal hemodynamics. Kidney Int 1988;33: 1147-55.
18. El Sayed AA, Haylor J, el Nahas AM. Mediators of the direct effects of amino acids on the rat kidney. Clin Sci (Colch) 1991;81:427-32.
19. Wada L, Don BR, Schambelan M. Hormonal mediators of amino-acid-induced glomerular hyperfiltration in humans. Am J Physiol 1991;260:F787-92.
20. Brezis M, Silva P, Epstein FH. Amino acids induce renal vasodilatation in isolated perfused kidney: coupling to oxidative metabolism. Am J Physiol 1984;247:H999-1004.
21. Lucchesi BR, Median M, Kniffen FJ. The positive inotropic action of insulin in the canine heart. Eur J Pharmacol 1972;18:107-15.
22. Svensson SE, Berglin W-O E, Ekroth R, Milocco I, Nilsson F, William-Olsson G. Haemodynamic effects of a single large dose of insulin in open heart surgery. Cardiovasc Res 1984;18:697-701.
23. Reikerås O, Gunnes P, Sörlie D, Ekroth R, Jorde R, Mjös OD. Haemodynamic effects of high doses of insulin during acute left ventricular failure in dogs. Eur Heart J 1985;6: 451-7.
24. Reikerås O, Gunnes P. Renal blood flow during acute ischemic heart failure in dogs: effects of dopamine and high doses of insulin. Scand J Clin Lab Invest 1986;46:671-5.
25. Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. J Clin Invest 1994;94:2511-5.
26. Cohen AJ, McCarthy DM, Stoff JS. Direct hemodynamic effect of insulin in the isolated perfused kidney. Am J Physiol 1989;257:F580-5.